Abstract

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Project Title: Discovery of Novel Allosteric Modulators of the M1 Muscarinic Receptor

Abstract: *DESCRIPTION* (provided by applicant): Evidence suggests that the antipsychotic effects of cholinergic agents may be mediated by the M1 or M4 subtype of muscarinic receptor. Previous compounds developed to selectively activate the M1 receptor have failed in clinical development due to a lack of true specificity for M1 and adverse effects associated with activation of other mAChR subtypes. Furthermore, the lack of highly selective compounds has made it impossible to definitively determine whether the behavioral and clinical effects of these compounds are mediated by M1 and M4 is also a viable candidate for mediating the antipsychotic effects. Previous attempts to develop agonists and antagonists that are highly selective for M1 or other specific mAChR subtypes have failed because of the high conservation of the ACh binding site and difficulty in developing compounds that are truly specific. Novel compounds have now been discovered that act at an allosteric site on M1 receptor rather than the orthosteric ACh-binding site to induce a robust activation of the receptor and provide high receptor subtype specificity. We have been highly successful in the use of high throughput screening technologies for discovery of novel allosteric ligands at multiple other GPCR subtypes. We have now developed a highly sensitive assay for the M1 muscarinic receptor that is suitable for high throughput screening of small molecule libraries for discovery of novel agonists and antagonists of this important GPCR. We propose a series of studies in which an M1 expressing cell line will be used by the MLSCN screening network to identify novel small molecules that act as agonists or antagonists at the M1 muscarinic receptor. Both agonists and antagonists can be identified in a single screen. We will then perform rigorous secondary assays to identify compounds that act at sites other than the orthosteric ACh binding site. Finally, we will use database mining and medicinal chemistry approaches to optimize selected compounds for use as laboratory reagents. Lay summary: The M1 muscarinic receptor is thought to be an important therapeutic target in schizophrenia. We have developed an assay system for high throughput screening to identify compounds with high selectivity for the M1 receptor subtype that act at an allosteric site on the receptor, thus providing increased specificity for this single receptor subtype. It is anticipated that these compounds will provide important tools for the study of muscarinic receptor function in the CNS.

Thesaurus Terms:
biological model, MLSCN, M1 Muscarinic Receptor, M4, mAChR, GPCR, High throughput screening, Allosteric Modulators, CNS

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